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PREVENTION OF INFLUENZA AND OTHER RESPIRATORY DISEASES (U)

ANNUAL PROGRESS REPORT

BY

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August, 1977
(For the period 1 November 1976 to 30 June, 1977)

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18. SUPPLEMENTARY NOTES

This report summarizes a study of a population of about 9000 individuals at Lowry AFB.

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

1) Illness rates due to the 1977 influenza A strains were low (about 5%) in unvaccinated young adults.
2) Illness rates were considerably lower in persons who had received vaccine containing 400 CCA units of A/Victoria/3/75.
3) Vaccine efficacy, by the lowest estimate, was 73%, and was probably considerably higher.
4) The new influenza A strain, as represented by A/Denver/1/77 did not spread into the surrounding civilian community.

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5) The data currently available indicate that A/Victoria/75 vaccine provided a high level of protection, and that a change in vaccine composition is not necessary.

6) A modest outbreak of influenza B occurred in the metropolitan Denver civilian community, and was reflected by a small number of cases of influenza B that occurred at Lowry AFB, primarily in permanent party personnel.

7) A significant rubella outbreak occurred during January and February, 1977, among both male and female students at Lowry AFB.

8) Despite outbreaks of influenza A and rubella, the incidence of febrile respiratory disease at Lowry AFB remain generally low. Adenovirus illness was virtually absent, and streptococcal pharyngitis occurred at only a low level.

9) Investigations are continuing to define the reasons for the unexpected HI antibody response to PR8 antigen in sera of students who received A/New Jersey/76 vaccine.

CONTENTS

1. Purposes of the Studies

a) To maintain surveillance of influenza A and B and to assess vaccine effectiveness in the event of outbreaks caused by swine-like strains or other variants.

b) To assess the effectiveness of current vaccines in eliciting antibody response to new influenza variants.

c) To assess the frequency and severity of adverse reactions following administration of the 1976 military influenza vaccine, containing 1300 CCA units of antigen, in Air Force personnel.

d) To determine the incidence of adenovirus disease in a vaccinated population with particular emphasis on the appearance of Type 21.

e) To determine the neuraminidase antibody response to vaccination and to assess the contribution which neuraminidase antibodies may make to the prevention of influenza illness.

f) To elucidate the unexpected appearance of high titers to PR8 antibody in persons who received recombinant (PR8) A/New Jersey/76 vaccine.

g) To determine the relative importance of various respiratory infections as causes of disability in recently inducted Air Force personnel.

2. Influenza A Vaccine Field Trial - Antigenic Drift and Influenza Vaccine Effectiveness

a) Introduction

The fundamental obstacle to the development of highly effective influenza vaccines is the continuing change in the antigenic composition of influenza A virus. This change occurs in two forms; first, an infrequent but major change in the viral hemagglutinin and sometimes also in the neuraminidase known as antigenic shift and, second, a frequent minor change in either or both of these viral capsid antigens called antigenic drift. The significance of antigenic shift was first observed in 1947 when H_0N_1 strains were replaced by H_1N_1 viruses. At that time the effectiveness of H_0N_1 vaccine was reduced to very low levels (1,2). An even greater change was observed in 1957 when the Asian pandemic occurred. The virus responsible for that outbreak (H_2N_2) differed in both its hemagglutinin and neuraminidase antigens from the earlier H_1N_1 strain. A third major change occurred in 1968 when the H_2N_2 viruses were replaced by H_3N_2 (Hong Kong) viruses. The effectiveness of Asian vaccine during the initial Hong Kong outbreak was reduced to approximately 40% (3).

Between these widely spaced episodes of major antigenic shift there occurs continuing drift. Since 1968 there has been a continuing change in the composition of the H_3N_2 virus. In 1972, when the so-called England strains appeared, Hong Kong virus vaccines provided approximately 60% protection (4). Further changes occurred in 1973,

when the Port Chalmers strains appeared, and in 1974, when the Scotland virus, which differed only slightly from Port Chalmers, became the prevailing strain. A sharper change occurred in the following year when the A/Victoria/75 strain became prevalent. A/Victoria/75 caused a sharp outbreak in the United States during the winter of 1975-76 with considerable excess mortality (5). A/Victoria/75 strains have been present during the 1976-77 season, but the incidence of disease appears to have been low. Further drift was noted during the winter of 1976-77 when strains now known as A/Texas/77 caused sharp outbreaks at two Air Force bases.

Vaccination against both influenza A and B has been routine for new military recruits for many years and annual revaccination has been practiced for members of the permanent military establishment. In line with this policy during 1976 all newly inducted personnel received a vaccine containing 400 CCA units each of A/Port Chalmers/73 and A/Scotland/75 until the month of October. At that time the vaccine composition was changed. Thereafter, all personnel received vaccine containing 400 CCA units each of A/New Jersey/76 and A/Victoria/75, and 500 CCA units of B/Hong Kong/72. When concern developed over the appearance of neurologic disease in recipients of the A/New Jersey/76 vaccine the program was suspended in mid-December 1976. No vaccine was administered to Air Force personnel until the middle of February 1977. For this reason a sizeable complement of unvaccinated individuals arrived at Lowry Air Force Base during this two month period from Lackland Air Force Base in Texas where an outbreak due to the new A/Texas/77 strain was first observed (6). Influenza occurred among these incoming troops and was introduced into the vaccinated population already stationed at the base. This unique circumstance made it possible to obtain information on the protective efficacy of vaccine containing the A/Victoria/75 antigen against the new influenza A variant.

b) Materials and Methods

Population Studied

The total population of the base numbered approximately 9000 of whom 4800 were members of the permanent party and 4200 were students. The students came to Lowry Air Force Base following recruit training at Lackland Air Force Base in Texas for approximately six weeks. After arrival at Lowry Air Force Base they were assigned within 2 or 3 days to one of the various schools for training courses which varied from six weeks to several months in duration. Students resided in barracks on the base and were divided into 12 training squadrons. Most were between 17 and 20 years of age and relatively few were more than 23 years old.

All students who had been on the base since approximately the first of November had received vaccine. However, those who had entered the Air Force after mid-December, after suspension of the National Influenza Immunization Program, were unvaccinated, and began arriving at Lowry Air Force Base after the end of January. Vaccination was not resumed on the base until the second week of March 1977.

The permanent party represented an older group and had relatively long assignments at the base. The majority resided off base in the Denver community and probably had more contact with the civilian population than did the students. Virtually all had received vaccine as part of the routine Air Force immunization program.

Vaccine

The vaccine administered from the latter part of October until the first week of December consisted of whole virus vaccine (Merck Sharp and Dohme Lot No. 4834G) which contained 400 CCA units of A/New Jersey/76 and 400 CCA units of A/Victoria/75 per 1.0 ml. Jet injectors were used to give 2 doses of 0.5 ml in one arm and concurrently in the other arm a 0.5 ml injection containing 500 CCA units of B/Hong Kong/72, a split virus vaccine prepared by Wyeth (Lot No. 173701).

Laboratory Procedures

Virus Isolation: Virus isolation was attempted from throat washings collected in beef extract broth. These were stored at approximately -5° in a refrigerator at Lowry AFB and transported within two or three days to the Virus Laboratory at the University of Colorado Medical Center. There they were treated with antibiotics, and inoculated into Rhesus monkey kidney tissue culture and a small number into 10-day old chick embryos by the amniotic route. Virus was detected in tissue culture by hemadsorption procedures and in chick embryos by red cell agglutination. Identification of virus strains as either influenza A or B was made by means of complement fixation test; strains were further typed by hemagglutination inhibition tests.

Serologic Procedures: Blood specimens were collected with voluntary informed consent from a very high proportion of individuals who reported with fever to the dispensary. Convalescent sera were collected 3 weeks later. Paired specimens were tested by complement fixation techniques using allantoic fluid antigens and by hemagglutination inhibition tests (7) against A/New Jersey/76, A/Victoria/3/75, A/Victoria/112/76, A/Texas/1/77, and A/Denver/1/77. The diagnosis of influenza was considered established when a virus was isolated and/or the individual showed a four-fold or greater increase in antibody titer in any of the tests.

Method of Surveillance

All personnel reporting to the dispensary with respiratory symptoms and a temperature of 99.6°F or higher were asked to report to the Influenza Study Office. There, clinical data were collected and efforts were made to obtain throat cultures and blood specimens with individual informed consent. Cooperation was remarkably good. Throat cultures were taken from virtually all patients at the dispensary laboratory for the diagnosis of beta-hemolytic streptococcal infections. A large number of samples were also collected from patients with rashes in the course of an unusually large rubella epidemic.

c) Results

1) Antibody titers following vaccination

Prevaccination titers of the study group could not be determined because vaccine had been administered at Lackland Air Force Base prior to the arrival of students in Denver. In order to obtain data on the distribution of post-vaccination antibody titers, sera from 74 individuals who reported with non-influenzal illnesses during the month of January were tested against three influenza A antigens and one influenza B antigen. The tests with the newly isolated 1977 influenza A strains were unsatisfactory with early passage allantoic fluids due to a relative lack of avidity and to the apparent presence of serum inhibitors. By the sixth passage however the newly isolated strains appeared to behave in a satisfactory manner (Table 1).

Virtually all individuals appeared to have satisfactory levels of antibody to the A/Victoria/75 strain from which the vaccine had been made. Highly satisfactory antibody responses were also seen to the 1976 strain, A/Victoria/112/76, and to the A/Denver/1/77 strain. The percent of individuals with titers of 8 or less was small in each group and there were very few individuals who had titers of less than 16. The proportion of individuals with very high titers for the new strains was somewhat lower than with A/Victoria/75. Only 67% had titers of >32 in tests with A/Victoria/112/76 and 75% in tests with A/Denver/1/77. A small number of tests with the strain A/Texas/1/77 showed results which were essentially interchangeable with those obtained with A/Denver/-1/77. It appeared therefore that the A/Victoria/75 vaccine had produced highly satisfactory levels of antibody in this population to the new influenza A strain.

The antibody response to the influenza B/Hong Kong/72 component of the vaccine was also highly satisfactory. Only 2% of individuals had titers of 8 or less.

2) Reactions following vaccination

Influenza A and B vaccines were given simultaneously. Because of the unfortunate decision to package influenza A vaccine in 0.5 ml doses, each containing 200 CCA units of A/New Jersey/76 and A/Victoria/75, it was necessary to give 2 jet gun injections one in one arm and one in the other. Virtually all recipients were seronegative for A/New Jersey/76 and for that reason it was anticipated that febrile reactions would occur among those who received 400 CCA units of whole virus vaccine. Prior experience suggested that there would be little reaction to the split virus influenza B component.

A tally was kept of the numbers of students reporting to the dispensary the following morning (about 18 hours later) with febrile reactions (Table 2). Among 2897 persons 3.8% were seen who had oral temperatures of 100°F or higher. Eight persons (0.3%) had temperatures of 102°F or higher and 2 persons had temperatures of over 103°F. No allergic reactions were recorded and no neurologic sequelae were observed.

3) The occurrence of influenza

Influenza B was detected in Colorado in December 1976 and during the next five months caused many outbreaks which affected primarily the younger segments of the civilian population, particularly in rural areas. Lowry AFB was unaffected until the second week of February when a number of students reported to the dispensary with classical findings of influenza. It soon became apparent, however, that the outbreak at Lowry was caused not by influenza B but by an influenza A virus which differed somewhat from A/Victoria/75. At the same time it was learned from Colonel George D. Lathrop, USAF Epidemiology Laboratory, Lackland Air Force Base, that Lackland AFB from which students were continually being sent to Lowry AFB, was also experiencing a sharp outbreak of influenza-like disease. During the following five weeks 85 cases of influenza A were confirmed at Lowry AFB and two more cases occurred later, with the last onset being on the 25th of March (Table 3). Influenza B was detected over a period of 8 weeks but there were never more than three cases per week. Virtually all cases of influenza B occurred in members of the permanent party who resided off the base in the Denver community and probably were exposed to the surrounding civilian population. On the other hand, the influenza A outbreak at Lowry AFB was not associated with any increase of influenza A in the civilian community. A comprehensive surveillance program detected only a single case of influenza A in Denver area civilians throughout this period.

Influenza spread rapidly throughout the base. Cases occurred in each of the 12 student squadrons, four squadrons had from 1 to 3 cases; the remainder had from 4 to 11 cases. Relatively high attack rates of 20 and 23 per 1000 per week were noted in unvaccinated personnel during the first two weeks of the outbreaks and thereafter rates fell off rapidly. In unvaccinated personnel the majority of cases tended to occur somewhat later and the rates at no time exceeded 2.1 per 1000 per week (Table 4).

4) Estimation of vaccine efficacy

Estimation of vaccine effectiveness is difficult because the population of the two groups was constantly changing as a result of the introduction of approximately 200 unvaccinated students per week. This had little effect on rates in the vaccinated population, which was large and was proportionally changing relatively less, but was far more significant in the unvaccinated segment of the population because it was rapidly enlarging and because most cases occurred in the first two weeks. For this reason three methods of estimating effectiveness were examined (Table 5).

The first was to divide the number of cases in unvaccinated personnel by the size of the group at the end of the study and to compare this with the number of cases in the vaccinated personnel divided by the number of persons at the beginning of the study. This gave the lowest possible rate of effectiveness and resulted in a figure of 69%. The second approach was to average

the rates per 1000 per week over the five weeks of the outbreak. This provided an estimate of vaccine effectiveness of 83.1%. The third approach was to base the estimate on the number of cases per person-weeks of exposure over a five-week period. With this method the vaccine efficacy was 80%. None of these methods can be regarded as absolutely precise in view of the relatively small numbers of cases and the shifting nature of the population. It appeared, however, that the protection obtained was of the order of 75-80%, a figure quite comparable to that observed in other outbreaks when the challenge virus was closely related to that administered in the vaccine.

5) Relationship between HI antibody titer and attack rate

Estimates of the relationship between attack rate and HI antibody titer at the time of illness was difficult because there was no sizeable group of vaccinated persons who had been vaccinated and bled at Lowry AFB. Among unvaccinated cases, 22 of the 24 cases occurred in persons with titers of 8 or less. No denominator was available to calculate an illness rate.

In vaccinated persons, sera were obtained from 74 persons who reported with illnesses other than influenza during the five weeks prior to the first detected case of influenza A. This group was used to estimate the percentage of persons at each titer level and the percentage figure was then extrapolated to the whole vaccinated student population in order to approximate the number of persons at each titer level. This number was then divided into the number of observed cases in order to obtain a rate at each titer (Table 6) in tests with the strain isolated from the outbreak (Denver/1/77).

Rates were considerably higher (4.1%) among persons with titers of 8 or less. Above this level there was little difference (0.6-0.4%) between the low rates observed over the titer range from 16 to 1024. The possibility that these high titers were caused by serum inhibitors was considered, but none of the currently used methods for treating sera to remove inhibitors produced any change in titer. Results were very similar when titers were measured with A/Victoria/75, suggesting that the cases were occurring mainly in persons who had escaped earlier infection with that virus. The almost uniform lack of complement-fixing antibody in the acute phase sera also suggested that these cases were occurring in persons who had not recently been infected with H_3N_2 viruses.

6) Characteristics of A/Denver/77 strain

The influenza A viruses isolated from this outbreak differed from strains isolated previously in the influenza A H_3N_2 family. They did not grow as readily as earlier strains. In contrast to several recent outbreaks, in which viruses were recovered from approximately 90% of individuals with confirmed influenza infections, the virus isolation rate was below 60% in this outbreak. This rate might have been higher if both chick embryos and monkey kidney had been

used, but relatively few specimens were inoculated in the former. The virus isolation rate was 52% from unvaccinated individuals and 60% from vaccinated individuals. Strains in the first few chick embryo passages were relatively non-avid, and for this reason were more readily identified as influenza A strains by complement fixation tests than by HI tests with specific antisera.

Data provided by Dr. Alan Kendal (8) of the Center for Disease Control, indicated that in tests with specific ferret antisera, viruses from this outbreak differed from A/Victoria/75 by 16-or 32-fold in both directions (Table 7), and most closely resembled the A/England/864/75 strain. There appeared to be no significant differences between the strains isolated in Denver, those isolated from Air Force personnel at Lackland AFB or from a civilian population in San Antonio where Lackland AFB is located.

7) Discussion

The aim of this study was to acquire data on the impact of antigenic drift on the effectiveness of influenza vaccine in preventing illness. This in turn bears directly on the question on what amount of antigenic drift is required before it is advisable to change vaccine composition from an older to a newer strain.

In 1977 the influenza A strains isolated in the Lackland AFB, Texas, and Lowry AFB, Colorado outbreaks appeared to differ sharply from the A/Victoria/75 strains from which the vaccine had been prepared. In tests with ferret antisera, crossed HI antibody tests showed major differences in each direction. However, ferret sera have long been known to be exquisitely strain-specific. When sera from humans immunized with the A/Victoria/75 vaccine were tested it was shown that, in contrast to the narrow responses observed with ferret antiserums, the antibody response was broad, probably reflecting earlier experience of this young adult population with influenza A viruses in the H_3N_2 family. The responses to the Denver/1/77 strain were in fact only slightly lower than to the A/Victoria/75 strain. Furthermore, the protective efficacy of the vaccine, approximately 80%, was comparable to that observed in the past with aqueous vaccines during outbreaks due to homologous viruses (9-11).

The situation in 1977 recalls that which existed in 1957 (9). At that time, at the end of the H_1N_1 period, virus strains designated as Denver or Netherland strains, which differed very sharply from earlier H_1N_1 strains caused an outbreak at Lowry AFB, but failed to produce a widespread epidemic in the civilian community. Vaccine prepared from an earlier H_1N_1 (A/AA/56) strain was shown to have a protective efficacy of 84% in spite of this divergence in the antigenic characteristics of the epidemic virus. This experience suggested that, after a virus family (e.g., all H_1N_1 viruses) has been present for many years, most persons who have reached adult age will have been infected at least once and that their response following vaccination with any member of that influenza virus family will be broad. They will also have a greater response in terms of HI antibody, neutralizing antibody

and resistance to infection than would persons who had not had exposure to that virus family. Neuraminidase antibody in all likelihood would also be boosted and may contribute to the prevention of illness.

While all past experience indicates that vaccine composition must be changed when an antigenic shift occurs, it appears that at least three factors deserve consideration before a decision is made to change vaccine strains. One factor is the duration of the period over which an influenza virus family has been present. When antigenic drift occurs soon after the appearance of a new family, for example, when the influenza A/England/72 strains replaced A/Hong Kong/68 strains, there is need for change because much of the population is not primed by prior infection and vaccine effectiveness will be reduced. By 1977, however, despite a drift which was of comparable magnitude when measured by tests with animal sera, the need was clearly less. A second factor in favor of changing vaccine strains is the demonstration by tests of sera of vaccinated humans that the old vaccine fails to produce a satisfactory response against the new strain. The human response is more relevant than that of the ferret or chicken. Finally, the capacity of an antigenic variant to spread and cause widespread epidemics must be considered. Many strains which are very different from prevailing ones appear and disappear without demonstrating the capacity to cause epidemics. This was the case with the A/Denver/77 strains in 1977. Strains of a very similar nature had been isolated in England as early as two years previously but had failed to spread widely. Much remains unknown about the characteristics of an influenza virus which enable it to spread and cause disease. In retrospect, this last point should perhaps have received greater weight when the decision was made to undertake the swine influenza vaccination program, for the A/New Jersey/76 virus, after causing a small outbreak at Fort Dix, showed no capacity to spread further in 1976 in a population in which the younger segment was essentially devoid of antibody.

8) Influenza A in permanent party

Estimates of illness rates in the permanent party are probably unreliable and tend to err on the low side because most reside off the base and may not report to the dispensary if their illness is mild. Nevertheless, the numbers reporting during influenza outbreaks invariably have risen, and this outbreak was no exception. During the five-week period of the vaccine study there were 29 confirmed cases among approximately 4860 personnel, an illness rate of just under 0.6% (Table 8). Cases occurred both in those persons assigned to training squadrons and those engaged in other activities on the base. The cases were concentrated during the last two weeks of the outbreak. The weekly attack rates at no time exceeded 2.0 per 1000 per week and cases were very similar to those observed in vaccinated students. All but three of the cases occurred in persons who had been vaccinated.

3. Influenza B

a) The Civilian Outbreak

Influenza B was first detected in Colorado in December, 1976 and cases continued to occur until May, 1977. Sharp outbreaks with high attack rates (over 30%) were reported in school populations in a number of rural communities, but in the Denver metropolitan area the disease followed a smoldering, endemic pattern. Cases in adults were infrequent and no substantial increase in the number of hospital admissions for pneumonia was observed.

b) Failure to Spread in Vaccinated Air Force Personnel

In spite of the continuing presence of influenza B in the community, the Lowry population experienced only a scattering of cases, 15 in all. Twelve of these occurred in permanent party personnel and only three in students. It was noted earlier(Table 1) that the levels of HI antibody following vaccination were very high in tests with B/Hong-Kong/72. It is probable that the number of cases would have been higher if vaccine had not been given, but this must remain speculative in view of the fact that there was no unvaccinated control group on the base.

c) Antibody Response in Patients

The influenza B strains isolated from patients grew readily and more rapidly in Rhesus monkey kidney tissue culture than did the A/Denver/77 strains. Viruses were isolated from 9 of 13 throat washings from serologically confirmed cases (69%). They were adapted with difficulty to chick embryos. The results of HI tests with serum pairs from 12 patients indicate that the B/Denver/77 virus was not that removed from B/Hong Kong/72 (Table 9). The lower titers observed with B/Denver/1/77 may simply reflect lack of avidity, a well documented characteristic of viruses in the B/Hong Kong/72 family. The acute phase antibody titers of vaccinated military personnel were often moderately elevated. In contrast, in a group of unvaccinated civilians acute phase antibody titers were uniformly low.

4. Respiratory Disease Rates in Students During 1976-77 Season by Etiologic Agents

Overall incidence of febrile respiratory diseases:

The incidence of febrile respiratory disease, as in the past 3 years, has been very low. Of a student population of approximately 4200 only 151 were seen at the dispensary with temperatures over 99^{0} during the period from 6 September to 2 January. The highest weekly rate during that period was 5.5 per 1000 per week.

During the period from 3 January to 29 April rates were somewhat more elevated reaching their highest points between 14 February and 14 March, when influenza A was occurring on the base. On only two occasions did rates reach a level of 10.2 cases per 1000 per week (Table 10).

Adenovirus illness was virtually absent, with only 5 cases detected. The very low level of adenovirus complement fixing antibody in the sera tested indicated that the student population had not experienced adenovirus disease at Lackland AFB. Oral vaccines have, in the past, been shown to produce little if any complement fixing antibody response.

Streptococcal pharyngitis was present throughout the season but the largest number of cases seen in any week was only 7. Influenza A was present over a seven week period between 7 February and 27 March. Influenza B occurred from 7 February to 19 April, but the maximal number of cases in any one week was only three. There were no periods of high incidence other than that associated with influenza A which might suggest an outbreak due to another agent.

A summary of the cases by etiology is presented in Table 11.

5. The Rubella Problem

Before the Christmas break a few patients reported with rashes. Sera collected from six patients showed that five had rubeola and one had rubella. Rubeola then disappeared. Early in January the number of patients with rashes rose sharply and high rates continued through February. Until the latter part of January these patients were not included in the respiratory disease study because they did not have respiratory symptoms. From February 1st on, however, all were interviewed and sera were collected. Their clinical course was typical of rubella. They were not seriously ill, and relatively few had much elevation of temperature. The 116 serum pairs collected in February represent only a portion of the 204 cases of rash disease recorded by the dispensary. It appeared that the outbreak was the largest in many years.

Sixty-two of the 63 paired serum specimens tested at the laboratories of the Colorado State Health Department showed significant rises in antibody titer for rubella, indicating that this was virtually a pure rubella outbreak. Eighteen percent of the cases occurred in female students; 25% of the student population is female. Few cases occurred in the permanent party.

In past years rubella has been observed to spread slowly through the student population, causing seroconversion of virtually all students with or without clinical illness. The desirability of immunization against rubella, after screening at the time of indication, seems clear. Morbidity from this disease, which was considerably greater than that from any of the respiratory diseases, could be eliminated and the risk of having rubella acquired during pregnancy could be avoided.

6. Unexpected HI Antibody Response to PR8 Antigen in Post-Vaccination Sera

In an earlier report it was noted that the HI antibody responses of individuals who had received the experimental X-42 vaccine were unexpected. This vaccine, which contained the hemagglutinin of A/Equi 1 and the neuraminidase of the A/Port Chalmers/73 failed to produce HI antibody to the Equi hemagglutinin except in very rare instances but did produce an increase in Port Chalmers antibody in a considerable proportion of individuals who lacked antibody prior to vaccination. This raised the question of whether the

Port Chalmers component had been completely eliminated in the recombination process or whether some type of combined hemagglutinin had been produced in which the Port Chalmers component had in some way become dominant. In the latter event the hemagglutinin obviously had not been removed by the steps of passing the recombinant through specific antiserum.

In view of these observations, when the sera from the experimental group which had received the A/New Jersey/76 vaccine became available, they were tested against not only A/New Jersey/76 but also against Port Chalmers and PR8 antigens. It was anticipated that there would be some evidence of cross between swine and PR8 in view of the earlier studies done by the Ann Arbor group but these were expected to be of a low order. It was a considerable surprise when it was shown that many individuals had not only equivalent titers against PR8 but that others had titers which were considerably higher (Table 12). There were, in fact, a considerable number of individuals who showed no response to A/New Jersey/76 but had high post-vaccination antibody titers against PR8. These individuals with few exceptions were below 19 years of age and had been born after the disappearance of H_0 and H_1 viruses.

Because the titer of our own laboratory PR8 pool was low, the first tests were run with a PR8 antigen provided by Dr. William Marine. This was an eluate used in earlier studies in England when he was engaged in studies of monovalent PR8 vaccine in children. In order to be certain of the identity of this antigen the same sera were again tested with our own PR8 strain and with a PR8 line received from the Center for Disease Control. Results are shown in Table 13. Essentially the same results were obtained regardless of the PR8 antigen which was used. As a further check on the identity of the Marine antigen six serum pairs from children who had been given monovalent PR8 vaccine were tested with the Marine antigen and with the Denver PR8 strain. Results are presented in Table 14. Again it appeared that the Marine and Denver antigens were behaving in an essentially identical manner.

At this point arrangements were made to send the sera to Dr. Kilbourne for testing and 15 serum pairs were selected from individuals who had shown no increase to antibody to A/New Jersey/76 but who had shown sharp rises in titer in tests with the PR8 antigens. Sometime passed before the sera were forwarded to Dr. Kilbourne and he communicated with us in June of 1977 that he could find no evidence of PR8 antibody in any of the sera. Consequently we reran the sera and failed to find any antibody with our own strain but found that the results with the Marine antigen were essentially the same as before, though the titers were perhaps a bit lower. We repeated this using in addition two PR8 antigens supplied by Dr. Kilbourne, one derived from the old Ann Arbor line and the other an English strain of PR8. The results again were the same with no antibody demonstrable with any of the PR8 strains except the one supplied by Dr. Marine (Table 15).

Puzzled by this finding and wondering whether the prolonged storage and repeated testing of these sera have in some way dropped the antibody titer, we selected a group of 20 serum pairs different from the ones tested earlier and ran them against four antigens, namely the Denver PR8 strain, Kilbourne's

Ann Arbor PR8, Center for Disease Control PR8, and the Marine antigen. With the first three antibody increases were demonstrable in a number of individuals and the results appeared to be interchangeable among the three strains used in the test (Table 16). Results with the Marine antigen were much as in earlier tests and differed only slightly from those observed with the three other PR8 strains. The titers obtained with the Marine antigen continued to drop slightly from those observed in earlier tests. It should be noted that this was an heterogenous group. A number of the sera came from young individuals who had received vaccine at Lowry AFB, a few from medical students at the University of Colorado Medical Center and a few from older persons who showed PR8 antibody in their prevaccination sera. All have been tested previously and had shown elevations of PR8 antibody titer to levels of at least 32 but several appeared to have lost antibody in tests with the regular PR8 strains.

Hopefully this rather puzzling finding can be clarified in the not too distant future. It is extremely important to characterize the nature of this response if we are to rely, as we have in recent years, on a recombination step in the preparation of vaccine.

7. Summary

1) Illness rates due to the 1977 influenza A strains were low (about 5%) in unvaccinated young adults.

2) Illness rates were considerably lower in persons who had received vaccine containing 400 CCA units of A/Victoria/3/75.

3) Vaccine efficacy by the lowest estimate was 73%, and was probably considerably higher.

4) The new influenza A strain, as represented by A/Denver/1/77 did not spread into the surrounding civilian community.

5) The data currently available indicate that A/Victoria/75 vaccine provided a high level of protection, and that a change in vaccine composition is not necessary.

6) A modest outbreak of influenza B occurred in the metropolitan Denver civilian community, and was reflected by a small number of cases of influenza B that occurred at Lowry AFB, primarily in permanent party personnel.

7) A significant rubella outbreak occurred during January and February, 1977, among both male and female students at Lowry AFB.

8) Despite outbreaks of influenza A and rubella, the incidence of febrile respiratory disease at Lowry AFB remain generally low. Adenovirus illness was virtually absent, and streptococcal pharyngitis occurred at only a low level.

9) Investigations are continuing to define the reasons for the unexpected HI antibody response to PR8 antigen in sera of students who received A/New Jersey/76 vaccine.

8. Acknowledgements

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Test Strain	Percent of persons with HI titer of: <8	8	16	32	64	128	256	512	1024	%≥16	%≥32
A/Vic/75	0	1	4	18	16	23	12	7	19	99	95
A/Vic/112/76	7	4	22	14	20	3	15	7	9	89	67
A/Den/1/77	4	5	16	32	8	15	9	4	5	90	75
B/HK/72	1	1	11	7	27	15	15	14	9	97	88

Table 1. Distribution of HI antibody titers of 74 vaccinated persons prior to outbreak in tests with 1975, 1976, and 1977 influenza A strains and with influenza B/HK/72.

Number Vaccinated	Number reporting on following day to dispensary with fever of:			
	99-99[8]	100-100[8]	101-101[8]	102
2897	63	65	37	8
	(2.2%)	(2.2%)	(1.3%)	(0.3%)

Table 2. Febrile reactions on day following vaccination.

week	Number of Cases of Influenza A	Influenza B
7-13 Feb.	11	2
14-20 Feb.	28	2
21-27 Feb.	12	2
28 Feb.-6 Mar.	22	1
7-13 Mar.	12	3
14-20 Mar.	1	1
21-27 Mar.	1	1
28 Mar.-4 Apr.	-	1
5-11 Apr.	-	1
12-18 Apr.	-	-
19-25 Apr.	-	1
total	87	15

Table 3. Number of cases of influenza by weeks in students and permanent party (1977)

	Unvaccinated Students			Vaccinated Students		
week	No. Cases	Pop.	Cases/1000/wk	No. Cases	Pop.	Cases/1000/wk
7-13 Feb.	6	295	20.0	3	3992	0.8
14-20 Feb.	12	509	23.6	8	3778	2.1
21-27 Feb.	1	696	1.4	8	3591	2.2
28 Feb.-6 Mar.	4	841	4.7	8	3446	2.3
7-13 Mar.	1	841	1.2	4	3446	1.2
total	24			31		

Table 4. Influenza A illness rates in unvaccinated and vaccinated students (Feb.-Mar., 1977)

Method of Calculation		No. of Cases	Rate	Estimate of Effectiveness
I. Maximum denominator in unvaccinated group		24	2.9	
Minimum denominator in vaccinated group		31	0.9	69%
II. Average of Rate/1000/week for 5 weeks	unvaccinated	24	10.2	
	vaccinated	31	1.7	83%
III. Total person-weeks of exposure for 5 weeks	unvaccinated	24	.0075	
	vaccinated	31	.0015	80%

Table 5. Estimation of vaccine effectiveness based on different methods of calculation.

HI Antibody titer	Estimated No. of Persons*	Observed No. of Influenza Cases	Estimated Attack Rate
8 or less	342	14	4.1
16-32	1824	11	0.6
64-128	874	4	0.5
256-1024	684	3	0.4

*Based on distribution of post-vaccination titers of 74 persons.

Table 6. Estimated attack rate in persons with different levels of post-vaccination HI antibody titers for A/Den/1/77.

	Ferret Antisera	
Antigen	A/Victoria/75	A/Texas/1/77
A/Vic/75	1280	80
A/Texas/77	80	2560
Difference	16-fold	32-fold

Table 7. Comparison of HI antibody tests with A/Vic/75 and A/Texas/77 vaccines using specific ferret antisera (data provided by Dr. Alan Kendal, CDC).

Week	No. of Persons	No. of Cases	Cases/1000/week
7-13 Feb.	4860	2	0.4
14-20 Feb.	"	8	1.6
21-27 Feb.	"	3	0.6
28 Feb.-6 Mar.	"	10	2.0
7-13 Mar.	"	6	1.2
Total		29	Attack Rate 0.6%

Table 8. Influenza A in the permanent party. Almost all had been vaccinated.

	Percent of persons with HI titer of							
Test Strain	<8	8	16	32	64	128	256	≥512
B/HK/72 Acute	6	-	2	2	1	-	1	-
Conv.	2	-	-	2	3	2	1	2
B/Den/77 Acute	5	1	3	1	-	2	-	-
Conv.	1	1	1	2	2	1	3	1

Table 9. Distribution of HI titers in 12 pairs acute and convalescent serums, tested against B/Hong Kong/72 and B/Denver/77.

Week of	Total Number	Rate/1000/week
6 Sept.	3	0.7
13	3	0.7
20	10	2.3
27	2	0.5
4 Oct.	4	0.9
11	7	1.7
18	10	2.3
25	7	1.7
1 Nov.	12	2.9
8	12	2.9
15	12	2.9
22	22	5.2
29	10	2.3
6 Dec.	23	5.5
13	21	2.3
20	13	0.9
27	-	---
TOTAL	151	
3 Jan.	6	1.4
10	17	4.0
17	17	4.0
24	31	7.4
31	21	5.0
7 Feb.	34	8.1
14	43	10.2
21	26	6.2
28	43	10.2
7 Mar.	37	8.8
14	30	7.1
21	24	5.7
28	17	4.0
4 Apr.	18	4.3
11	14	3.3
18	11	2.6
25	7	1.7
TOTAL	396	

Table 10. Number of cases of febrile (>99[6]) respiratory diseases in student population during the 1976-77 season.

Period	Influenza A	Influenza B	Strep.	Adeno.	Rubella
Before Christmas	--	--	18	2	1 (+ 5 -- Rubeola)
Total classified/total tested -- 26/131					
After New Year week of					
3 Jan	--	--	--	--	2
10	--	--	4	--	1
17	--	--	6	--	1
24	--	--	3	--	17
31	--	--	6	--	6
7 Feb.	11	2	7	--	18
14	28	2	5	1	31
21	12	2	2	--	6
28	22	1	1	1	9
7 Mar.	12	3	3	--	5
14	1	1	4	--	6
21	1	1	3	--	2
28	--	1	5	--	3
4 Apr.	--	1	4	1	2
11	--	--	2	--	--
18	--	1	3	--	1
25	--	--	1	--	0
TOTAL	87	15	59	2	110
Total classified/total tested -- 274/396 (69%)					

Table 11.
Classification by etiology of febrile respiratory diseases and rashes from specimens received for laboratory diagnosis, 1976-77 season.

Source of Vaccine	Test Strain	% of persons with titers of 8 or less	16-32	64-128	256-512	1024 or more	% with 4-fold rise
M.S.D.	A/NJ/76	28	48	11	9	4	72
	PR8	16	11	19	33	20	83
M.N.	A/NJ/76	58	22	11	4	4	40
	PR8	67	4	16	9	4	33
Wyeth	A/NJ/76	54	17	14	5	10	42
	PR8	78	8	7	5	2	22
P.D.	A/NJ/76	73	2	15	6	4	27
	PR8	67	13	8	4	8	33

Table 12. Comparison of post-vaccination HI antibody to A/NJ/76 and PR8 of persons under 25 years of age and seronegative before vaccination: (groups numbered 45 to 59 persons)*

*Meiklejohn, G., Eickhoff, T.C. Prevention of Influenza and Other Respiratory Diseases. Annual Progress Report to the U.S. Army Medical Research and Development Command. August, 1976.

Pre- and post vaccination H.I. antibody titer

No. of Test	1		2	
Date	5/27/76		6/24/76	
Antigen	A/NJ/8/76	PR8 (Marine)	PR8 (Denver)	PR8 (CDC)
Vaccinee				
1	<8/16	16/1024	8/256	<8/128
2	<8/32	<8/512	<8/256	<8/256
3	<8/16	<8/512	<8/512	<8/512
4	8/32	<8/<8	<8/128	<8/32
5	<8/16	<8/32	<8/16	<8/8
6	<8/16	<8/512	<8/512	<8/512
7	<8/128	<8/128	<8/256	<8/128
8*	<8/<8	<8/<8	<8/<8	<8/<8
9	<8/1024	<8/256	<8/128	<8/128
10*	<8/<8	<8/<8	<8/<8	<8/<8
11	<8/<8	<8/256	<8/256	<8/128
12*	<8/<8	<8/<8	<8/<8	<8/<8
13	<8/256	<8/1024	<8/1024	<8/1024
14	<8/16	<8/512	<8/128	<8/128
15	<8/128	<8/1024	<8/1024	<8/512
16*	<8/<8	<8/<8	<8/<8	<8/<8
17	<8/16	<8/128	<8/64	<8/128
18	<8/32	<8/32	<8/32	<8/16
19	<8/512	<8/256	<8/128	<8/256
20	<8/<8	<8/128	<8/128	<8/128
Antisera PR8	<8	512	256	512
A/NJ/8/76	512	<8	<8	16

*Received placeb

Table 13. Comparison of H.I. antibody response following A/NJ/8/76 vaccine in tests with A/NJ/8/76 and 3 PR8 antigens, Marine, Denver and CDC.

Percon	H.I. antibody titer in test with PR8 (Denver)	PR8 (Marine)
1	<8/512	<8/128
2	<8/1024	<8/256
3	<8/1024	<8/512
4	<8/64	<8/32
5	<8/512	<8/512
6	<8/512	<8/128

Table 14. H.I. antibody response of 6 children who received monovalent PR8 vaccine in tests with Denver PR8 strain and PR8 eluate provided by Dr. William Marine.

	Post-vaccination HI antibody in test with PR8 antigen			
	Denver	Kilborne (AA)	CDC	Marine
Vaccinee				
1	<8	<8	<8	256
2	"	"	"	128
3	"	"	"	256
4	"	"	"	64
5	"	"	"	256
6	"	"	"	64
7	"	"	"	64
8	"	"	"	64
9	"	"	"	32
10	"	"	"	512
11	"	"	"	256
12	"	"	"	<8
13	"	"	"	<8
14	"	"	"	<8
15	"	"	"	128
PR8	1024	1024	1024	1024
A/Vic/75	8	16	8	16
B/HK/72	<8	<8	<8	<8

Table 15. Results of test of 7/1/77 with 4 PR8 antigens. All these convalescent sera had shown titers of 32 or greater in previous tests with PR8 and CDC antigens.

Pre- and post-vaccination HI antibody with PR8 antigen

Vaccinee	Denver	Kilbourne (AA)	Kilbourne (Eng)	Marine
1	<8/<8	<8/<8	<8/<8	<8/128
2	<8/256	<8/128	<8/128	<8/256
3	<8/<8	<8/<8	<8/<8	<8/128
4	8/1024	8/1024	8/1024	8/1024
5	<8/8	<8/<8	<8/<8	<8/256
6	<8/<8	<8/<8	<8/<8	<8/512
7	<8/256	<8/64	<8/128	<8/128
8	16/128	32/128	32/128	64/256
9	16/128	64/64	64/128	64/512
10	16/1024	<8/1024	<8/512	16/1024
11	<8/256	<8/128	<8/64	<8/256
12	<8/64	<8/<8	<8/<8	<8/256
13	16/256	8/128	8/128	16/512
14	256/512	256/256	256/256	512/1024
15	16/128	16/128	32/128	64/1024
16	32/64	32/32	32/32	32/64
17	512/1024	128/256	256/256	512/512
18	32/1024	16/1024	-	32/1024
19	64/128	32/64	32/64	64/256
20	32/32	<8/16(?)	32/32	32/32
PR8	1024	1024	1024	1024
A/Vic/75	8	8	8	16
B/HK/72	<8	<8	<8	<8

Table 16. Results of test of 7/21/77 with PR8 antigens on paired sera for 20 persons who had received A/A7/76 vaccine. These sera are from persons not included in Table 3.

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